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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/492,954	01/27/00	PYLE A	58077/JPW/JS

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EXAMINER	
WILDER,C	

ART UNIT	PAPER NUMBER
1655	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/492,954	Applicant(s) Pyle et al.
	Examiner CB Wilder	Group Art Unit 1655

☒ Responsive to communication(s) filed on *Jan 2, 2001*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-8* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, filed January 2, 2001 (Paper No. 7), is acknowledged. Claim 1 has been amended. Claims 1-8 are pending. The arguments have been thoroughly reviewed but are found not persuasive for the reasons that follows. Any rejection not reiterated in this action have been withdrawn as being obviated by the amendment of the claims.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action.

Previous Objections and Rejections

3. The objections to the drawings and the specification are withdrawn in view of Applicant's amendment. The claim rejections under 35 U.S.C. 112 second paragraph drawn to claims 1-6 as being indefinite is withdrawn in view of Applicant's amendment of the claims and arguments. The prior art rejections under 35 103(a) drawn to claims 1-8 are maintained.

Claim Rejections - 35 USC § 103

4. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuman (Proc. Natl. Acad. Sci. USA, November 1992), in view of Bjornson et al. (Biochemistry, December 1994) and further in view of Eggleston et al. (Nucleic Acids Research, April 1996). Regarding claim 1, Shuman discloses a method for detecting the release of a single-stranded RNA from an RNA duplex

which comprise (a) admixing an RNA helicase with the RNA duplex under conditions permitting the RNA duplex to unwind the RNA duplex and release single stranded RNA, wherein the RNA duplex comprises a first RNA having a label and a second RNA wherein the unwound single-stranded RNA released from the duplex is detected by gel electrophoresis (page 10936 col. 1, lines 18-29 and 40-52, see Figure 1 and Figure 2). The method of Shuman differs from that of the claimed invention in that Shuman does not teach wherein the first label is capable of producing a luminescent energy pattern when the first RNA is present in the RNA duplex which differs from the luminescent pattern produced when the first RNA is not present in the RNA duplex. The reference also does not teach detecting a change in the luminescent energy pattern produced by the first label to thereby detect release of a single-stranded RNA from the RNA duplex. Bjornson et al. (Biochemistry, December 1994) teach a method for detecting the release of a single stranded DNA molecule from a DNA duplex comprising admixing a helicase with a DNA duplex under conditions permitting the helicase to unwind the duplex and release single stranded DNA, wherein the first strand of the DNA substrate I has a label attached thereto at the 3' end and the second strand of the DNA substrate I has a label attached thereto at its 5' end, wherein the first label is capable of producing a luminescent energy pattern, detecting changes in the luminescent energy pattern produced by the first label so as to thereby detecting release of single-stranded DNA from the DNA duplex (page 14309, last paragraph col. 1 to first paragraph col. 2, see also page 14310, Figure 2). Bjornson et al. teach several advantages of using a fluorescent based assay for kinetic studies in general and particularly for mechanistic studies for helicase-catalyzed unwinding. First, such an assay is extremely sensitive

(Abstract), allowing unwinding to be monitored continuously in real time. Second, a full kinetic time course can be obtained from a single experiment with more accurate determination of the observed kinetic parameters. Third the data can be easily imported into numerical simulation programs and fourth, one can perform an experiment over a much wider range of substrate concentrations (page 14312, col. 1, lines 112-44). Although Bjornson et al. do not mention the fluorescent assay being used for detecting single stranded RNA from RNA duplexes, Bjornson et al. do mention that the advantages of a fluorescent based study will greatly facilitate the detailed kinetic studies that are needed to understand the mechanism(s) by which helicases (implying both RNA and DNA helicases) carry out their essential function (page 14313, col.2, first paragraph). Eggleston et al. teach a method similar to that of Bjornson et al. for detecting the release of nucleic acid molecules from nucleic acid duplexes. Eggleston et al. teach wherein fluorescent dyes as label molecules are used to monitor unwinding of duplex DNA and RNA (page 1180, col. 2, first full paragraph). Eggleston et al. further state that it is possible to monitor the process of DNA or RNA unwinding by measuring the decrease in florescence as the dye ligands are displaced from the duplex molecules (page 1180, col. 2, first full paragraph). The authors teach that although their studies focused on DNA helicases, the fluorescent assay provides a new means by which the unwinding activity of RNA helicases can be examined. Eggleston et al. further state that their results suggest that fluorescent detecting of unwinding is possible for RNA helicases (page 1185, col. 2, first full paragraph) and that fluorescent methods for detailed studies of kinetic mechanisms are ideal because they provide continuous data in real time (page 1179, col. 2, last 2 lines at bottom of page). In view of the foregoing, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to have been motivated to modify the RNA detection method of Shuman by incorporating a label useful in a fluorescence based assay as taught by Bjornson et al. and Eggleston et al. to detect the release of single stranded RNA from the RNA duplex instead of a radiolabel. One of ordinary skill in the art would have been motivated to do so by the teaching of Eggleston et al. that fluorescent based assays can be readily adapted for use with DNA helicases, RNA helicases and other enzymes that act on nucleic acid to monitor nucleic acids unwinding (Abstract). Additionally one of skill in the art would be motivated to incorporate a label which produces a luminescent energy pattern instead of a radiolabel for the obvious benefits which includes cost-effectiveness, commercial availability and non-toxicity.

6. Applicants arguments filed in Paper No. 8 have been fully reviewed and considered. Applicant traverses the rejections on the following ground: Applicant summarizes the invention and states that Shuman teaches a method of detection by gel electrophoresis of RNA unwinding which uses a radiolabel attached to a RNA strand. Applicant argues that Shuman does not teach the use of a label which produces a luminescent energy pattern. Applicant further argues that Bjornson et al. teach a method for detecting the release of a single stranded DNA molecule from a DNA duplex. Applicant argues that the Examiner appears to have applied an "obvious to try" standard on the present case. Applicant states that "an ordinary skilled artisan would recognize that there would be no reasonable expectation of success in a method of detecting RNA unwinding using a label which produces a luminescent energy pattern based on the teaching of a method using a radiolabel attached to an RNA

strand in combination with the teaching of a label capable of producing a luminescent energy pattern when attached to a DNA strand. Applicant further argues that one of skill in the art would recognize that RNA presents obstacles to success that are not present with DNA and for which the Applicants' claimed invention provides a solutions. Finally, Applicant concludes that the cited references, either alone or in combination, even if motivating one to try the Applicant's claimed invention would not present a reasonable expectation of success.

7. These arguments have been thoroughly reviewed but they are not found persuasive for the reasons that follows: In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference of Shuman teaches detecting the release of ssRNA from an RNA duplex comprising the use of RNA helicase under conditions which permits the release wherein the RNA duplex comprises multiple radiolabels and detection is monitored using gel electrophoresis. The secondary reference of Bjornson et al. teach the use of fluorescent labels in energy transfer assays to monitor the release and unwinding of ssDNA from DNA duplexes using helicases. The reference of Bjornson et al. teach several advantages of using florescent based assays to monitor unwinding of DNA instead of the methods using radiolabels and electrophoresis. Bjornson et al. teach the the

fluorescent based study will greatly facilitate the detailed kinetic studies that are needed to understand the mechanisms bu which helicases (implying both RNA and DNA helicases) carry out their function. Further motivation for using the fluorescent labels in the method of detecting release of RNA by RNA helicases is provided in the teachings of Eggleston et al. that fluorescent based assays can be readily adapted for use with DNA helicases, RNA helicases and any other enzyme that acts on nucleic acids to monitor DNA or RNA unwinding. Eggleston further teach that fluorescent based methods are advantageous for detailed studies of kinetic mechanisms because they provide continuous data in real time. Therefore, in contrast to Applicant's arguments, one of ordinary skill in the art would expect with a reasonable expectation of success that the use of fluorescent labels instead of radiolabels could be used to monitor the unwinding and release of RNA from RNA duplexes. Applicant's arguments did not provide sufficient evidence to overcome the prior art rejection under 103(a). Accordingly the rejection is maintained.

Regarding claim 2, Shuman discloses wherein the conditions which permit the RNA helicase to unwind the RNA duplex and release the single stranded RNA comprise the presence of ATP and a divalent cation, e.g., Mg^{2+}, Co^{2+}, and Mn^{2+} (page 10936, col. 1, lines 40-52).

Regarding claim 3 and 4, Bjornson et al. teach wherein a label is present at the 3' end of the first stand of the DNA and a different label is attached to the second strand of the DNA at the 5'end and the luminescent energy pattern results from the interaction of luminescent energy released from the two different labels (page 14309 col. 2, lines 1-28 see also Figure 1).

Regarding claim 5, Bjornson teach wherein the two labels comprise fluorophors and the second label absorbs luminescent energy released from the first fluorophor (page 14309, Figure 1).

Regarding claim 6, Bjornson et al. teach wherein the first label is fluorescein (donor) and the second label is hexachlorofluorescein (acceptor) (page 14309, Figure 1 and 14310, Figure 2). The choice of a first and second label would have been determined by the skilled artisan based on commercial availability, experimental procedures and desired results.

Regarding claim 7, Bjornson et al. disclose a method of measuring the rate of release of DNA from a DNA duplex which comprise detecting whether single stranded DNA is released from the duplex at predetermined time intervals and determining the rate of release of the single stranded DNA from the duplex (page 14310, Figure 2 and col. 2, first and second full paragraphs).

Regarding claim 8, Shuman discloses a method of determining whether a compound is capable of modulating the release of a single stranded RNA from an RNA duplex by an RNA helicase which comprise detecting the release of the single stranded RNA from the RNA duplex, wherein the compound (AMPPNP or AMPPCP) is added to the mixture comprising the RNA helicase, RNA duplex and label (page 10937, figure 5).

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Cynthia Wilder whose telephone number is (703) 305-1680. The Examiner can normally be reached on Monday through Thursday from 7:00 am to 5:00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Exr.'s supervisor, W. Gary Jones, can be reached at (703) 308-1152. The official fax phone number for the Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed the Group's receptionist whose telephone number is (703) 308-0196.

Cynthia B. Wilder

Cynthia B. Wilder, Ph.D.

March 7, 2001

W. Gary Jones
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3/9/01